PATENT ABSTRACTS OF JAPAN

(11)Publication number : 11-005742

(43)Date of publication of application : 12.01.1999

(51)Int.Cl. A61K 31/575
A61K 7/00
A61K 7/48

(21)Application number : 09-218288

(22)Date of filing : 30.07.1997

(71)Applicant : SHISEIDO CO LTD

(72)Inventor : SATO JUNKO
DENDA MITSUHIRO
KOYAMA JUNICHI

(30)Priority

Priority number : 09117508 Priority date : 21.04.1997 Priority country : JP

(54) EXTERNAL PREPARATION CONTAINING CHOLESTEROL SULFATE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject dermal external preparation for controlling decomposition of desmosome in the skin by including a cholesterol sulfate.

SOLUTION: This external composition is obtained by including a cholesterol sulfate (cholesterol 3-sulfate ester) derived from a living body or partially or totally synthesized at approximately 0.005 to 20 wt.%, based on the whole composition, preferably 0.5 to 5 wt.%, for lotion, cream or the like, and further including a diluent or aid (alcohol, water, chelating agent, urea, surfactant or the like) which is commonly used for cosmetics and external medicines.

LEGAL STATUS

[Date of request for examination] 29.05.2002

[Date of sending the examiner's decision of rejection] 28.03.2006

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

DERWENT-ACC-NO: 1999-136702

DERWENT-WEEK: 199915

TITLE: Cholesterol sulphate containing composition - used to inhibit desmosome decomposition to accelerate epidermal desquamation and renewal of corneal layer

PATENT-ASSIGNEE: SHISEIDO CO LTD[SHIS]

PRIORITY-DATA: 1997JP-0117508 (April 21, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP **11005742** A	January 12, 1999	N/A	004	A61K 031/575

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP 11005742A	N/A	1997JP-0218288	July 30, 1997

INT-CL (IPC): A61K007/00, A61K007/48 , A61K031/575

ABSTRACTED-PUB-NO: JP 11005742A

BASIC-ABSTRACT:

External dermal composition (especially for inhibition of desmosome decomposition, or for maintaining epidermal normal balance between decomposition and inhibition of desmosome) contains cholesterol sulphate (CS) as the active ingredient.

USE - The CS-containing composition can inhibit desmosome decomposition to accelerate epidermal desquamation and renewal of corneal layer.

ADVANTAGE - CS can antagonistically inhibit activities of both serine protease (trypsin-like enzyme and chymotrypsin-like enzyme) in desmosome to balance the formation and decomposition of desmosome in accordance with epidermal

condition.

CHOSEN-DRAWING: Dwg.0/1

TITLE-TERMS: CHOLESTEROL SULPHATE CONTAIN COMPOSITION INHIBIT DECOMPOSE
ACCELERATE EPIDERMIS RENEW CORNEA LAYER

DERWENT-CLASS: B01 D21 E15

CPI-CODES: B01-D02; B14-D07C; B14-N17; D08-B09A; E01;

CHEMICAL-CODES:
Chemical Indexing M5 *01*
Fragmentation Code
M781 M903 M904 P943 S005 S032 S131 S133 S134 S142
S143 S303 S317 S703 S750 S752 S761 S762 U560 U563
Specfic Compounds
11954U

Chemical Indexing M2 *02*
Fragmentation Code
C216 K0 K4 K442 M210 M211 M271 M282 M320 M416
M620 M781 M903 M904 M910 P943
Specfic Compounds
00274K 00274U
Registry Numbers
0274U

Chemical Indexing M3 *02*
Fragmentation Code
C216 K0 K4 K442 M210 M211 M271 M282 M320 M416
M620 M781 M903 M904 M910 P943
Specfic Compounds
00274K 00274U
Registry Numbers
0274U

UNLINKED-DERWENT-REGISTRY-NUMBERS: 0274U

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1999-040366

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the pharmaceutical preparation for dermatology, especially skin external preparations.
[0002]
[Background of the Invention] Conventionally, in order to maintain the treatment and the fresh skin of a certain fixed skin disease, various kinds of moisturizers and use of lipids including cholesterol have been tried (about use of cholesterol, they are G.Lykkesffldt et al., Lancet, 1983, and 1337 -1338 reference).
[0003] If the knowledge relevant to cholesterol is surveyed here, it is known for the ichthyosis caused by the deficit of steroid sulfas TAZE that the hyperkeratosis will be held with are recording of a cholesterol sulfuric acid. Moreover, the thing of extent which can be viewed without accompanying partial spreading of a cholesterol sulfuric acid by erythema for which it can drop and ** is brought about is also reported (M. E.Maloney et al., J.Invest.Dermatol., 83 (1984), 252-256).
[0004] however, especially in the hoof which has a strong adhesive property, a cholesterol sulfuric acid exists in abundance (P. -- M.Elias et al. --) J. between the horny layer (palm) pasted up closely and the horny layer (overarm) pasted up loosely, to Clin.Invest.74 (1984) and that [1414-1421] It is reported that there is no significant difference (S. Serizawa et al., J.Invest.Dermatol., 99 (1992), 232-236). Anyway, the relation between a cholesterol sulfuric acid and the accumulated horny layer is not necessarily clear.
[0005] On the other hand, the desmosome in the skin has the role important for adhesion of a keratin cell, and it is checked that decomposition of the desmosome by two sorts of serine proteases (a trypsin Mr. enzyme and chymotrypsin Mr. enzyme) brings about the desquamation of a horny layer (for example, Y.Suzuki et al., British J.Dermatol., 134 (1996), 460-464). Based on such knowledge, the persons involved in this invention person proposed a means to harmonize formation and its physiological exfoliation of a horny layer, by promoting the two above-mentioned sorts of serine protease activity.
[0006]
[Problem(s) to be Solved by the Invention] By the way, probably, the activity of the above-mentioned serine protease may be required when unusually, and control of those activity holds the homeostasis of the skin conversely.
[0007]
[Means for Solving the Problem] As a result of having examined the matter which has such depressant action, in the experiment of the capacitation of a sperm, the cholesterol sulfuric acid with which checking those serine proteases is also reported found out controlling the enzyme activity of desmosome.
[0008] In this way, the cholesterol sulfuric acid found out that it could be intentionally used for controlling the decomposition activity, when superfluous decomposition of desmosome had arisen.

Therefore, in order to solve the above-mentioned technical problem here, the skin external preparations which come to contain a cholesterol sulfuric acid as an active principle are offered, and the skin external preparations for controlling decomposition of the desmosome which comes to contain a cholesterol sulfuric acid as an active principle are offered. Moreover, the skin external preparations for maintaining the normal balance of the decomposition of desmosome and control in the skin which comes to contain a cholesterol sulfuric acid as an active principle as invention of another mode are offered.

[0009] As invention of further another mode, the positive desquamation in the skin which comes to contain a cholesterol sulfuric acid as an active principle is brought about, and the skin external preparations for promoting renewal of a horny layer are offered.

[0010] As for the cholesterol sulfuric acid (namely, cholesterol 3-sulfate) used by this invention, the thing of the living body origin may also be obtained by the semisynthesis and the total synthesis. These are marketed and should just use what can come to hand easily to this contractor.

[0011] Although a cholesterol sulfuric acid can be used with the diluent or assistant regularly used as cosmetics or medical-application external preparations, these diluents etc. must not have a bad influence on an operation of a cholesterol sulfuric acid. As a typical thing of a diluent or an assistant, alcohol, water, a buffer, a chelating agent, a urea, a surfactant, etc. can be mentioned.

[0012] Although a cholesterol sulfuric acid can fluctuate the content to the inside of external preparations according to dosage forms and the concrete purpose of use, in the case of a lotion, cream pharmaceuticals, etc., it can be included 0.5 to 5% of the weight preferably about 0.005 to 20% of the weight per total constituent weight. Moreover, those preparation can be carried out according to the well-known approach as the method of preparation of various skin external preparations.

[0013] In this way, since the cholesterol sulfuric acid as an active principle controls both the activity by the trypsin Mr. enzyme and chymotrypsin Mr. enzyme in desmosome in antagonistic inhibition, as for the external preparations of this invention obtained, it is possible to make formation and decomposition of desmosome balance according to a skin condition.

[0014]

[Example] Hereafter, an example explains this invention and its operation effectiveness still more concretely.

(Effect of partial spreading)

Experiment cholesterol sulfuric acid Sigma What came to hand from the shrine was used, and the 8-weeks old male was used for the hair loess mouse (HR-1) three groups.

[0015] 80micro of 10 cholesterol sulfuric-acid (following, CS) solutions L of mM in dimethyl sulfoxide (DMSO) was applied behind the hair loess mouse once per day. The horny layer was collected by tape stripping three days after. Moreover, it carried out by uniting a biopsy.

[0016] The <histological observation> biopsy sample was fixed with formalin 10%, and embedding was carried out to paraffin. Hematoxylin-eosin staining of the intercept was carried out. The thickness of epidermis was measured with the optical microscope (Olympus XL-10) equipped with the image analysis system.

[0017] It fixed with the fixing fluid of KARUNOFU skiing, and the biopsy sample was processed with 1.0% osmium tetroxide of reduction, and carried out embedding to resin. After carrying out electron staining of the ultrathin section with citric-acid lead and uranium acetate, it observed with the electron microscope (H7100, Hitachi). The horny layer was counted by the bride method.

[0018] a result -- the epidermis by partial spreading of CS to a mouse, and change (1) of a horny layer The scale which will be visible behind [whole] a mouse after spreading of CS on the 3rd was generated.

[0019] (2) A difference was not accepted between the DMSO processing whose thickness of epidermis is a basis, and CS processing.

[0020] (3) The number of layers of the horny layer under an electron microscope was increasing by about 1.5 times by CS processing compared with DMSO processing.

[0021] (Detection of the desmosome of a horny layer)

200micro buffer solution containing 0.1M Tris HCl (pH9), 9M urea, 2%SDS, and 1% mercaptoethanol

of buffer solutions per 2mg of horny layers (L) extracted from the horny layer which carried out tape stripping and extracted the protein of experiment desmosome at 37 degrees C for 15 hours. Extract Laemmli It mixed with the sample buffer solution (Laemmli et al., Nature 227 (1970) 680-685), and heated on the water bath for 10 minutes. Supernatant liquid was analyzed by SDS-PAGE (10% gel) after centrifugal. Electrophoresis gel was moved to the PVDF film (Applied Biosystems), and desmosome protein was detected by the Western blot technique using the antibody to the DESUMO grain I.
The content of the DESUMO grain I in the horny layer of a result CS processing mouse was higher than basis DMSO processing. This result shows that decomposition of desmosome is controlled by partial spreading of CS. Specifically, please refer to drawing 1 .
[0022] (Distribution of the cell from a horny layer sheet)
experiment horny layer sheet 1mg -- kanamycin 60micro -- 37 degrees C incubated for 24 hours in g content cleaning agent mixed liquor [dimethyl dodecyl amine oxide [of 8mM] (DMDAO) and 2mM sodium dodecyl sulfate (SDS)] 1ml. Respectively, the horny layer sheet was agitated for 2 seconds with the vortex mixer after the incubation performed including CS (1mM, 5mM), DMSO, and a protease inhibitor (0.25mM chymostatin and 0.25mM leupeptin). The number of the cells which have separated in cleaning agent mixed liquor was measured by the haemacytometer.
[0023] Compared with the time of distribution of a result cell adding DMSO, it became clear that it would be controlled to 19.6% if it adds by 5mM to 51.9%, and distribution of a cell would be controlled by the concentration dependence target in CS if it adds by 1mM. In addition, in addition of a protein inhibitor, distribution of a cell was suppressed to 1.3%.
[0024] (Operation over the trypsin and chymotrypsin of CS)
The experiment crystal Buta pancreas trypsin (Wako) and the crystal cow pancreas chymotrypsin (Sigma) were used, and the inhibition behavior of CS was investigated. In addition, the homologous of the trypsin Mr. enzyme of desmosome and a chymotrypsin Mr. enzyme, and an amino acid sequence chose these proteases from the very high thing, respectively [above-mentioned Suzuki's and others reference and Skytt et al., Biochem.Biophys.Res.Comm., 211 (1995), and 586 -589 reference].
[0025] Trypsin activity and chymotrypsin activity were measured as a substrate using Boc-Phe-Ser-Arg-MCA (3107-V) and Suc-Leu-Len-Val-Tyr-MCA (3120-V) (peptide lab), respectively. All assays were performed at 37 degrees C among 0.1M Tris HCl (pH8.0).
[0026] Result CS showed antagonistic inhibition also to which of a trypsin and KIMOTORIPUKIN, and the inhibition constant was 2.1microM to 5.5microM and a chymotrypsin to the trypsin.
[0027] If the above is summarized, it is expected that inhibitory action is shown to the protease in a horny layer, and CS is in vivo. Producing a scale is checked, while controlling decomposition of desmosome then and thickening a horny layer.
[0028]
(Example of a formula)
Presentation (% of the weight)
Stearyl alcohol 6.0 Stearin acid 2.0 Hydrogenation lanolin 4.0 Squalane 9.0 An octyl dodecanol 10.0 Cholesterol sulfuric acid 1.0 1, 3-butylene glycol 6.0 polyoxy ethylene glycol 1500 4.0 Polyoxyethylene (25) cetyl alcohol 3.0 Glyceryl monostearate 2.0 antiseptics Optimum dose Antioxidant Optimum dose Perfume Optimum dose Purified water A moisturizer is added to 54.0 preparation purified water, and heating adjustment is carried out at 70 degrees C. After the heating dissolution, a cholesterol sulfuric acid, a surfactant, antiseptics, an antioxidant, and perfume are added, and oil is adjusted to 70 degrees C. This was added to the previous aqueous phase, it makes an emulsification particle into homogeneity and cooled [deaerated, filtered and] in the homomixer, and the cream was obtained.
[0029]
[Effect of the Invention] If it is used when decomposition of superfluous desmosome is obtained, returning it to a normal condition is expected and the skin external preparations which include CS as an active principle will be able to be used for maintaining the normal balance of decomposition of desmosome, and control, so that I may be understood from an operation of the above CS.

[Translation done.]